CLINICAL AND IMMUNOLOGICAL PROFILE IN

NEWLY DIAGNOSED HIV PATIENTS

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"CLINICAL AND IMMUNOLOGICAL PROFILE IN NEWLY DIAGNOSED HIV PATIENTS"** submitted by **Dr.N.RAJASEKAR** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch I (General Medicine) is a bonafide research work was carried out by him under my direct supervision & guidance.

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DECLARATION

I, **Dr.N.RAJASEKAR** declare that, I carried out this work on, **"CLINICAL AND IMMUNOLOGICAL PROFILE IN NEWLY DIAGNOSED HIV PATIENTS"** at the Department of Medicine, Govt. Rajaji Hospital during the period of February 2011 to October 2012. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

Place : Madurai **Dr.N.RAJASEKR**

Date :

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CONTENTS

INTRODUCTION

Simian immunodeficiency virus (SIV) was prevalent among chimpanzees for several thousands of years. For unknown reasons it had remained silent without harming humans. During the middle of twentieth century, it had transformed into Human Immunodeficiency virus. Numerous hypotheses have been forwarded for explaining this phenomenon. In most of the theories, colonisation of African nations, rapid urbanisation, unprotected sex and travel were being attributed for the sudden transformation and spread. [1][2] After transformation it had taken only few years for the pandemic to get established.

Today the virus has spread worldwide and has become a biggest public health challenge for low income countries. As it primarily affects working population of a nation, it has resulted in a great economic burden. Infections which were previously uncommon and sporadic, are being frequently reported. Several countries are witnessing resurgence of tuberculosis.

HIV is one of the most extensively studied virus. Thousands of articles are being published each year about HIV/AIDS. This has led to immense knowledge about the virus as well as the disease. Epidemiological data, statistics and guidelines are regularly updated by international bodies. Mandatory screening with effective testing methods have effectively brought

down blood products related transmission to a negligible rate. Active campaigns about HIV have resulted in increased awareness among public. Global annual new HIV infection rate have started to decline. Treatment regimens have been changed to improve the drug compliance as well to minimise adverse effects. Now patients are able to lead a normal life like any other person with the help of effective therapeutic regimens. In developed nations like United States, many patients who are under treatment remain asymptomatic for more than two decades.

Despite all these achievements in the field of HIV/AIDS, most of the studies from around the world show that greater proportion of PLHA is being diagnosed at very late stages. Initiation of ART in early stages has shown to improve the life expectancy and reduce the risk of opportunistic infections (OIs). In fact newer guidelines are promoting initiation of drugs at higher level of CD4 counts (at 500/µl).

Diagnosing PLHA at early stages has thus become an essential step to utilise the maximum benefits available. CDC has recommended including HIV screening in routine basic blood investigations performed during a health visit. In conditions like papular pruritic eruptions and immune thrombocytopenic purpura, diagnosis of HIV must always be considered. As the patient becomes symptomatic after a long latent period, one of the earliest symptoms would be frequent upper respiratory tract infections. Clinical

profile of HIV/AIDS patients varies in different geographical regions. Kaposi sarcoma which is very common in Africa and United States has been rarely reported from India. Common mode of transmission also varies between countries and also within a nation. Homosexuals carry high risk for acquiring HIV in USA whereas heterosexual route is the commonest mode of transmission in India. Injection drug users have high risk for HIV acquisition in north eastern states of India. Thus for practising physicians it becomes necessary to know about various presenting clinical manifestations of HIV.

AIM

1. To study about the clinical profile of HIV at the time of diagnosis.
2. To study about the mean CD4 count among newly diagnosed HIV patients.
3. To study about the correlation between CD4 count and the various clinical parameters.

HISTORY

The existence of an immunodeficiency disease was first suspected in 1981 in USA. This was after publication of several articles about cases of Pnuemocystis carnii pneumonia in a group of young homosexual men. [3] The disease was soon named as GRID- Gay related immunodeficiency disease. [4] Later it was found to be prevalent also in non gay population. CDC later coined the term acquired immunodeficiency syndrome (AIDS)

Luc Montaignier was the first to isolate HIV from lymphoid ganglions for which he was awarded Nobel Prize. He named it as Lymphadenopathy-associated-virus (LAV). Later Robert Gallo proved that AIDS is infact caused by LAV. He named the virus as human T-cell lymphotrophic virus-3(HTV-3). Later CDC coined the term Human immunodeficiency virus (HIV).

Earliest documentation of HIV was from a specimen (taken on 1959) of a Congolese man. HIV was detected from his preserved blood sample. But whether he developed AIDS was not known.

ELISA test became the first serological test for detection of HIV. During late 1980s Lamivudine was approved by FDA for treatment of HIV. Later protease inhibitors and other drugs came to the market which had revolutionised the management of HIV/AIDS thereby leading to drastic decline in morbidity and mortality as well as improvement in quality of life.

The staggering global epidemic has been well matched by prolific scientific advances in the field of HIV including virology, immunology, pathophysiology, diagnostics, treatment and vaccine development. [5]

EPIDEMIOLOGY:

Globally around 34 million are affected with HIV infection. About 30 million people died so far since the onset of this epidemic. Although HIV is prevalent all over the world, almost all cases are from middle and low income countries especially sub-Saharan Africa. There is a declining trend in global epidemic with decrease in number of new cases reported as well as reduction in number of AIDS related death.

Latest global statistics:[6]

Total Number Of PLHA:	34.0 Million
Prevalence rate(for ages between 15–49) :	0.8%
People died of AIDS In 2011:	1.7 million
New HIV infections in 2011 :	2.5 million

According to recent statistics from National AIDS control organisation (NACO),[7] approximately 24 lakh people are affected with HIV/AIDS in India. Tamil Nadu which is one of the high prevalent states for HIV now accounts for about 150,000 cases. In 2009 , about 172000 died because of

HIV in India. Now annual HIV incidence in India has been reduced dramatically. Recent analysis showed there is a 50% decline in new incidence of HIV. In 2000 the number of new infections reported were 270,000 whereas in 2009 it has been reduced to 120,000. [8]

VIROLOGY:

HIV belongs to family retroviridae and genus lentivirus. The following viruses comes under this family.[8]

1. HTLV-1 which causes tropic spastic paraparesis and Adult T- cell leukemia
2. HTLV-2 which is more common than HTLV-1 but no disease has yet been reported
3. HIV-1 which causes AIDS
4. HIV-2 which also leads to AIDS but much less common than HIV-1

MORPHOLOGY OF HIV:

Virion : Spherical in shape.

80–100 nm in diameter.

It has cylindric core.

Envelope: Present

Inner nucleocapsid contains viral genome and also various enzymes including reverse transcriptase and integrase. Outer envelope contains many spikes which represents membrane glycoproteins. The envelope contains two important protein that play vital role in binding of virus to host cell membrane. They are gp120 and transmembrane protein gp41. The outer membrane contains not only viral proteins but also host proteins that are derived during budding process. Host proteins that are commonly found are MHC class I and II antigens.

Outstanding characteristics of HIV:[9]

1. Predominantly affected cells: cells involved in immune function
2. Permanent association of provirus within the infected cells.
3. Expression of virus: restricted in some cells in vivo.
4. Long clinical latency: Disease progresses very slowly
5. Replication: species-specific.

VIRAL GENOME:

The viral genome has following characteristics, It is made up of ribonucleic acid (RNA).It has two single stranded positive sense RNA particles. It is 9kb in length. It codes for nine genes. The nine genes are gag, pol, env, tat, rev, nef, vif, vpr and vpu. In HIV-2 vpu is replaed by vpx.[10]

GENETIC DIVERSITY AND CLASSIFICATION OF HIV:

HIV is broadly divided into two types HIV-1 and HIV-2, of which HIV-2 is uncommon and epidemiologically less significant when compared to HIV-1.One of the unique characteristics of HIV-1 is its high degree of genetic diversity. Now to name different strains of the virus six categories are being used [11].

1. GROUPS
2. SUBTYPES
3. SUB-SUBYPES
4. Circulating recombinant forms
5. Unique recombinant forms
6. Geographically distinct lineages

GROUPS:

It includes M,N,O and P. Group M is the commonest cause of HIV around the globe. It has further been classified into various clades, subsubtyes and CRFs.

SUBTYPES:

Group M divided into various clades: A,B,C,D,E,F,G,H,J,K2

SUB-SUBTYPE**:**

Subtypes A and F are divided further into A1, A2, F1 and F2. Subtypes B and D does not show much genetic variation from each other and in fact should be included in sub-subtypes, but they are retained in subtypes itself in order to avoid confusion.

CIRCULATING RECOMBINANT FORM (CRF) :

These are hybrid strains formed in an individual who has dual infection with two different strains.

GEOGRAPHIC DISTRIBUTION OF VARIOUS HIV STRAINS [12]

1.	Sub-Saharan Africa	Subtype C (most common) Subtype B and G, CRFO2_AG
2.	India	Subtype C
3.	China	Subtypes B, C and BC recombinant forms
3.	Southeast Asia	CRF01_AE
4.	North America and some parts of South America	Subtype B
5.	Australia	Subtype B
6.	Western Europe	Subtype B
7.	Eastern Europe	Subtype A,B and AB recombinant forms

New emerging strains:[13]

Thai B. Indian C.	southern China*
CRF03_AB	Former soviet union
CRF14_BG	Spain* Portugal*
BF recombinant forms	South America
CRF35_AD	Afghanistan and Iran*

*predominantly among injection drug users

INITIAL PATHOGENESIS:

HIV enters through a breach in the mucous membrane. It binds to resting CD4 cells in lamina propria. It also binds to the surface of dendritic cells through specialised C-type lectin receptors called DC-SIGN.[14] Success rate of sexual route transmission is very low because of sparsely distributed CD4 cells in lamina propria. The dendritic cells are then carried to draining lymph nodes where it facilitates binding of virus to CD4-T Lymphocytes. CD4 cells may exist in two forms [15]. 1) Resting state. 2) Activated state. CD4 cells are polyclonal group of cells which are usually quiescent and when body is exposed to microorganisms, individual clones are activated in response to specific antigenic stimuli. So during infectious states, activated CD4 cells are increases. In HIV there is also a non specific activation of all clones of CD4 cells.

Activated CD4 cells are characterised by high rate of DNA replication, transcription and translational process. If HIV is integrated into genome of such cells, it also undergoes high degree of replication.

PROTEINS THAT PLAY VITAL ROLE IN INITIAL PATHOGENESIS [16]

Gp120	CD4 receptor ligand. Appears like numerous spikes over the envelope of the virion
Gp 41	Transmembrane protein in the virion. Penetrates host membrane and coil upon itself thereby helping in fusion
CD4	Surface protein over T lymphocytes
CCR5	A beta chemokine receptor over host cells like lymphocytes , dendritic cells, macrophages and glial cells
CXCR4	Predominat coreceptor used by HIV during late stages of infection

FUSION:

Gp120 present over the virion gets attached to CD4 molecule which is found predominantly in T helper cells. The protein undergoes conformational change. This leads to exposure of underlying protein Gp41. This is present beneath Gp120. It also results in binding of host cell through co-receptors CCR4/CXCR5. Gp41 penetrates the host membrane, thereby bringing together viral and cellular membrane resulting in fusion.

FOUNDER VIRUS:

Not all viruses of infected individual has ability to transmit disease. It is to be noted that once infection is disseminated and established the virus

during its replication in various lymphoid tissues acquires extreme genetic diversity. So there is a high degree of variation in genetic characteristics and immunological response of existing virus in the plasma and the initial founder virus [17]

CHARACTERISTICS OF FOUNDER VIRUS

1. Short V1-V2 loop
2. Minimal N-linked Glycosylation
3. Underrepresentation in the plasma viremia of TP*
4. Limited genetic diversity
5. Rapid divergence after transmission
6. Presence of effective neutralizing antibodies in TP*

*TP-Transmitting partner

The virus after infecting CD4 cells of draining lymphoid organ (in case of blood borne transmission spleen is the initial organ affected). Later it gets disseminated into other lymphoid organs. One of the primary target for he virus is Gut Associated Lymphoid Tissue (GALT). GALT is rich in CD4 cells. Infection and depletion of all CD4 cells in GALT indicates that infection has been widely disseminated and firmly established.

IMMUNE SYSTEM EVASION OF HIV

Despite the most effective and potent immune mechanism s possessed by human beings , Human Immunodeficiency virus escapes all the defence mechanisms and continue to survive within the host, thereby creating a great challenge to the scientific world to eradicate the virus from the infected individual.

Some of the mechanism by which the virus evades immune system are mentioned below. [18]

1. Presence of latently infected cells acts as a reservoir of infection. These cells remain dormant until activated

2. HIV is extremely recombinogenic. The rapid burst of viral replication results in extreme degrees of genetic variation within the viral population. So antibodies produced by immune system may not be effective in neutralizing the virus because of rapid selection process by the virus.

3. CD4 Helper cells play a central role in antigen driven specific immune response to a foreign antigen. Antigen presenting cells present foreign antigen to CD4 cells through MHC molecule. This activates the antigen specific clones of CD4 cells. These activated cells promote production of antibodies and stimulate cytotoxic T lymphocytes. As mentioned earlier, HIV actually infects and depletes CD4 cells resulting in immunocompromised state

4. HIV can transfer from one cell to another through virological synapses. This protects the virus from exposure to immune mechanisms

5. For infected cells to be recognised and eliminated by CD8 cells, infected cells should express MHC molecule over its surface. But in HIV infected cells these molecules are poorly expressed because of underrepresentation.

Mechanism of immune evasion by Gp120 from neutralizing antibody

1.	Conformational masking of antigenic epitopes
2.	High degree of glycosylation of the protein
3.	Presence of hypervariable regions

PROTEINS WITH ANTIVIRAL ACTIVITIES IN HUMAN CELLS:

1. APOBEC3G

2. TRIM5α

3. TETHERIN

APOBEC3G:

It causes suppression of viral transcription. [19] It acts on viral genome and substitute adenosine in the place of guanine in the viral genome. The virus can easily overcome its action by ubiquitinisation and degradration of the protein. This is carried out by vif gene.

TRIM5α:

This protein causes premature uncoating of viral nucleocapsid in cellular cytoplasm itself.[20] Virus evades this cellular antiviral mechanism by producing variation in capsid protein

TETHERIN:

This is a newly found molecule present in the host cytoplasm.[21] It is otherwise called CD317. It inhibits budding of newly formed virus through cellular membrane. Viruses are sequestered in tetherin mediated vesicles. Action of tetherin is inhibited by increased production of vpu protein by the virus

MODE OF TRANSMISSION

Common modes of transmission of HIV are

1. SEXUAL ROUTE

2 .BLOOD AND BLOOD PRODUCTS

3. MOTHER TO CHILD TRANSMISSION

4, INJECTION DRUG ABUSE

5. TRANSMISSION TO HEALTH PERSONNELS

SEXUAL TRANSMISSION:

This is the commonest mode of transmission of HIV around the globe although this is much less efficacious method than other routes. Among all high risk groups, MSM (men having sex with men) carry highest risk of acquiring the infection. Historically HIV was named GRID i.e., Gay Related Immunodeficiency and was believed to be an immunosuppressive disease of male homosexuals.

Females carry higher risk of acquisition of virus during a vaginal intercourse than males. This is because of relatively longer duration of exposure of female genital tract to infected seminal fluid.

Risk factors for HIV transmission

1.	High viral load in transmitting partner
2.	Multiple sex partners
3.	Serodiscordant partners
4.	Unprotected sex
5.	Uncircumcised individuals
6.	Presence of sexually transmitted diseases
7.	Anal intercourse

In the presence of sexually transmitted diseases, genital ulcerations provide the necessary mucosal breach for entry of HIV. So the risk of HIV transmission is high in the presence of STDs. In addition, STDs and also urinary tract infections can cause infiltration of genital tracts (which usually are sparsely distributed with inflammatory cells in the absence of STDs) with various inflammatory mediators including T lymphocytes thereby facilitating entry of virus into host cells.

Circumcision has been shown to decrease the risk of transmission. Circumcision in a HIV patient has been shown to reduce the risk of transmission to serodiscordant spouse. [22]

Factors responsible for high risk in circumcised individuals

1. Absence of protective keratin in inner layer of foreskin
2. Foreskin is rich in dendritic cells (antigen presenting cells) which are carriers of the virus
3. High incidence of STDs in uncircumcised individual
4. High susceptibility of microtrauma to foreskin during sex

Plasma viral load is directly proportional to risk of transmission. Reducing plasma viremia using antiretroviral therapy (ART) has been shown to reduce the risk of transmission. Presence of high quantity of HIV RNA in genital tract has been shown to increase the risk of transmission.

Use of oral contraceptive pills (OCPs) has also been shown to increase the risk of HIV transmission. OCPs alter the characteristics of cervical mucosa thereby increasing the risk of viral entry. [23]

TRANSMISSION BY BLOOD AND BLOOD PRODUCTS:

The first case of blood borne transmission of HIV happened in 1978 in a haemophiliac patient.[24] Since then it became the most dreaded and inevitable disease among haemophiliacs for almost a decade. There was a gradual decline in incidence of HIV among haemophiliacs following the discovery of serological assays and mandatory screening of all blood products before transfusion.

Despite the effective screening measures for all the blood products, still there is a minimal residual risk for transmission. Although the transmission rate has been brought down drastically it has never been brought to zero. Despite the major advances that had been achieved in science in so far, techniques are still lacking to detect HIV during the initial period of infection (window period)

Before the introduction of nucleic acid assays (NAT), the window period was more than a month. Now it has been reduced to less than two weeks. This risk can also be eliminated by eliciting a detailed history from the donors. Health personnel must ask all donors about symptoms suggestive of acute HIV seroconversion. Donors must be asked about their recent sexual activities.

In some countries (like the United States and France) where MSM is one of the common mode of transmission, male homosexuals are prohibited from donating blood. This has led to marked decline in blood borne HIV transmission. [48]

TRANSMISSION BY ORGAN TRANSPLANTATION:

HIV transmission has been reported in all types of solid organ transplantation.[26] Organ donation by HIV patients has been prohibited worldwide. There is growing debate to lift his ban thereby allowing HIV patients to donate organ HIV positive individuals who are in need of transplant. This will increase the availability of organs for transplantation.

Methods to reduce transplantation related transmission[26]

1. Excluding high risk donors
2. Processing of organs before transplantation to inactivate the virus
3. Repeating serological tests after two weeks to exclude seroconversion

MOTHER TO CHILD TRANSMISSION:

Factors increasing the risk of transmission:

1. High plasma viral load
2. Low maternal CD4 count
3. Prolonged duration of labor
4. Premature rupture of membranes
5. Chorioamnionitis
6. Procedures facilitating spontaneous delivery

Perinatal period carries highest risk of transmission which is followed by antenatal and postnatal period. Breast feeding has been recommended in developing countries in all HIV positive mothers under the

cover of antiretroviral therapy. Antiretroviral therapy has been recommended in all pregnant women with HIV irrespective of viral load and CD4 count.

Factors that reduce risk of transmission:[26]

1. Antenatal screening of all mothers during her first visit
2. Prenatal counselling for HIV positive couples
3. Initiation of ART during pregnancy
4. Caesarean delivery

CLINICAL FEATURES:

HIV produces a spectrum of clinical manifestations ranging from asymptomatic state to severe AIDS wasting syndrome. Patient may either present with opportunistic infections or manifestation due to the virus per se like HIV encephalopathy.

ACUTE HIV SYNDROME:[27]

It develops after three to six weeks of infection in more than half of the affected individuals. The symptoms are mostly self limiting and last only for few weeks. Because of acute reduction in CD4 counts, even OIs have been reported. In IDUs symptoms like fever, sore throat, exanthems, malaise are uncommon.[28]

Approximately one in ten infected individual will progress to fulminant disease. Sometimes patient deteriorate after recovering from acute illness.

Clinical manifestation during acute infection

Systemic symptoms:

Fever	Pharyngitis
Myalgia	Arthralgia
Weight loss	Nausea
Vomiting	Diarrhea
Headache	Retroorbital pain
Lymphadenopathy	

Cutaneous manifestations

Mucocutaneous ulcers	Erythematous maculopapular rash

Neurological manifestations:

Encephalitis	Aseptic meningitis
Acute transverse myelitis	Peripheral neuropathy
Acute demyeliniating Encephalomyelitis [29]	

ASYMPTOMATIC STAGE:

After initial state of plasma viremia and acute HIV syndrome, symptoms of the patient disappear and there is acute recovery of immune function. During initial stages there may be increase in the count of total CD8 cells.[30]

In this stage there is a steady decline in CD4 count. The count decreases by 50 per year. Patient may be clinical latent even for a decade. But it does not mean microbiological or immunological latency. There is a continual destruction of immune system as well as progressive increase in viral load as time advances even during asymptomatic state.

LONG TERM SURVIVORS:

Some patients will remain asymptomatic even after very long time. There are four such groups.

1. LONG TERM NON PROGRESSORS (LTNPs):

They are characterised by following features [31]

Very low plasma viral load.
Normal CD4 count.
Prolonged asymptomatic period that may last for more than two decades.
Not on ARTs

2. ELITE CONTROLLERS:

These are special group of LTNPs. They are characterised by[32]

Extremely low plasma viral load.
Normal CD4 count
Strong immune response to virus
Overrepresentation of HLA class I molecules.

3. Patients on ART:

Antiretroviral therapy had made an immense advance in this century. Newer drugs and regimes have enabled the patients to live a longer and healthier life. These groups can be called as long-term-non-survivors. But they cannot be termed as LTNPs.

4. Fourth group includes patients who are asymptomatic despite the declining immune status. Unlike in the above three groups where CD4 is normal here it continues to decrease. These groups suddenly manifest with opportunistic infections

SYMPTOMATIC STAGE:

There are two different international classification system for staging clinical presentations of HIV /AIDS. One is by CDC (Centre for disease control). It classifies the disease into three stages. In India, NACO follows

WHO staging. It classifies the disease into four stages. The fourth stage includes all AIDS defining illnesses.

Stage 1:

Asymptomatic patients.
Persistent generalised lymphadenopathy.

Stage 2:

Moderate unexplained weight loss.
Mucocutaneous manifestations:
1. Papular pruritic eruptions.
2. Seborrheic dermatitis.
3. Angular cheilitis.
4. Herpes zoster.
5. Onychomycosis.
6. Recurrent oral ulcers.
Recurrent Respiratory tract infections:
1. Sinusitis.
2. Bronchitis.
3. Otitis media.
4. Pharyngitis.

STAGE 3:

1. Severe weight loss.
2. Unexplained chronic diarrhea
3. Unexplained persistent fever
4. Oral candidiasis
5. Oral hairy leukoplakia
6. Pulmonary tuberculosis
7. Severe bacterial infections
8. Unexplained anemia
9. Unexplained thrombocytopenia

STAGE 4:

1.	HIV wasting syndrome
2.	Pnuemocystis pneumonia
3.	Recurrent severe or radiological bacterial pneumonia
4.	Chronic herpes simplex infection
5.	Esophageal candidiasis
6.	Extrapulmonary tuberculosis
7.	Kaposi sarcoma
8.	CNS toxoplasmosis

9.	HIV encephalopathy

Stage 4 Conditions which require confirmatory tests

1.	Extrapulmonary cryptococcosis
2.	Disseminated non tuberculous mycobacteria
3.	Visceral leishmaniasis
4.	Crytosporidiasis
5.	Isosporiasis
6.	Invasive cervical carcinoma
7	Candida of trachea, bronchi and lung
8.	CMV infection
9.	Lymphoma
10.	Recurrent non typhoidal salmonella sepsis
11.	Progressive multifocal leukoencephalopathy
12.	Any disseminated mycosis

Diseases of respiratory system:[34]

1. Sinusitis:

- It is usually caused by bacterial agents.
- It may involve any sinuses. Patients respond very well to antibiotics.
- Rarely mucormycosis may be the cause. It can cause invasive sinusitis.
- In such cases, amphotericin-B and emergency debridement are indicated.

2. Pneumonia:

It is one of the commonest complications of HIV. It occurs early during the course of infection. Dysfunction of neutrophils and plasma cells are common in HIV patients. So there is a high susceptibility to capsulated organisms

Common agents causing pneumonia:

Bacterial:

1. Streptococcus pneumonia.
2. Hemophilus influenza.
3. Staphylococcus aureus.
4. Pseudomonas aeruginosa.

Fungal :

1. Pneumocystis jiroveci.
2. Other fungal agents: Rhodococcus, Coccidiodes, Histoplasmosis

Pneumococcal vaccine has been recommended in all individuals despite the immune status. In all other individuals the dose must be repeated every five years.

PNEUMOCYSTIS CARNII PNEUMONIA:[35]

It is the commonest case of pneumonia among PLHA in the United States. In about half of these cases individuals were not aware that they are HIV positive. In most of the cases, CD4 count is less than 200.

Clinical features:

- Fever.
- Non productive cough.
- Dyspnea.
- Unexplained weight loss.

Lab features:

- Chest x ray: Normal/ Bilateral interstitial infiltrates.

  Rarely pleural effusion.
- CT thorax: It may show ground glass opacities.
- ABG: Hypoxia and acidosis can occur in severe cases.

- Demonstration of organisms:

1. Special staining of sputum/ bronchoalveolar lavage (eg. Methenamine silver stain)
2. Immunofluoresence staining of specimens with monoclonal antibodies.
3. PCR for DNA amplification.

Extrapulmonary manifestations:

These are common in patients on aerosolised pentamidine therapy. Some of the common extrapulmonary involvement are mentioned below

- Ear: Polypoidal mass in the outer ear.
- Eye: choroidal lesions.
- Skin : necrotising vasulitis.
- Bone marrow hypoplasia.
- Intestinal obstruction.
- Cystic or healed calcified lesions in liver, spleen, kidney, heart and pericardium.

Treatment:

Trimethoprim-sulphamethaxazole is the treatment of choice.. Other alternative drugs that can be used are mentioned below.

1. Trimethoprim+Dapsone.
2. Atovaquone.

3. Clindamycin+Primaquine.
4. Pentamidine.
5. Trimetrexate+Leucovorin.

Patients should be treated for 3 weeks. Corticosteroids are indicated in severe disease. Steroids if used must be initiated as early as possible. Presence of PCP is an indication for initiation of antiretroviral therapy.

Prophylaxis:

Co-trimoxazole is the agent of choice for both primary and secondary prophylaxis. Other agents that can be used are mentioned below.

1. Once a day dapsone.
2. Weekly therapy with Dapsone+Pyrimethamine+Leucovorin.
3. Once a day Atavoquone.
4. Once a month Pentamidine nebuliser therapy.

TUBERCULOSIS:

Tuberculosis has become one of the greatest public health challenge around the world, especially in developing countries. Developed

nations are witnessing a resurgence of tuberculosis following HIV pandemic. It is responsible for approximately 33% of deaths among AIDS population. PLHA have about hundred fold increased risk for acquiring the disease when compared to normal population.

Immune activation by Mycobacterium tuberculosis(MTB):

As previously mentioned HIV replicates only in activated immune cells. Mycobacterium tuberculosis by producing IFN and various other cytokines activate immune system. Latent viruses also are activated and undergo active replication thereby resulting in increased viral load. During the process of replication and active production of virions, lymphocytes are destroyed thereby causing reduction in CD4 cells. Thus tuberculosis co-infection can accelerate the course of HIV infection. [36]

Clinical and radiological features:

There is a wide spectrum of manifestations. Symptoms and signs vary according to CD4 count. [37]

CD4 count	Features	Remarks
High CD4 count	Apical tuberculosis	Weight loss, night sweats, fever, cough common

Low CD4 count	Disseminated disease	Diffuse lower lobe disease. Bilateral reticulonodular opacities. Pleural effusion. Bilateral hilar adenopathy. Sputum may be negative for AFB.
Low CD4 count	Extrapulmonary tuberculosis	Meningitis. Tuberculous lymph node. Osteomyelitis. Abdominal tuberculosis.

Sometimes patients may even be asymptomatic. So all PLHA must be screened during initial evaluation. In endemic countries like India, all PLHA must be screened annually.

INVESTIGATIONS:

1. Sputum AFB staining: negative results do not rule out PT.
2. Sputum culture for MTB.
3. PPD (purified protein derivative) test.
4. Blood culture : in cases of disseminated tuberculosis.
5. Chest X ray: varied presentation as discussed earlier.
6. Drug susceptibility testing: to rule out drug resistant strains.

Initiation of ART must be done either after ruling out tuberculosis or after initiation of antituberculous agents. Otherwise it may lead to IRIS (Immune reconstitution Inflammatory syndrome).

TREATMENT:

ATT is started just like any other patients. Rifampin is an inducer of CYP450. Some of the protease inhibitors and NNRTIs are also metabolised through the same pathway. So rifamfin should be avoided. Rifabutin is preferred. ART must never be started before starting treatment for tuberculosis

PREVENTION:

WHO has recommended several preventive measures.

The three ‘I’s recommended by WHO[38]	
1.	Intensified case finding
2.	Isoniazid preventive therapy
3.	Infection control

ATYPICAL MYCOBACTERIAL INFECTION:

Common agents:

1. Mycobacterium avium.
2. Mycobacterium intracellulare.

Clinical features:

1. Fever
2. Weight loss
3. Abdominal pain
4. Diarrhea
5. Lymphadenopathy

Lab features:

1. Chest x ray: bilateral lower lobe infiltrates.
2. Positive blood culture.
3. Reduced haemoglobin.
4. Raised alkaline phosphatase.

Treatment:

Clarithromycin plus ethambutol combination is preferred. In addition rifabutin/ciprofloxacin/amikacin can be added.

Prophylaxis:

When CD4 <50/µl.

Drugs preferred: Azithromycin 1200 mg/ week.

Clarithromycin 500 mg bd.

OTHER RESPIRATORY DISEASES

Idiopathic interstitial pneumonia:

1. Lymphoid interstitial pneumonitis.
2. Nonspecific interstitial pneumonitis.

Neoplastic disease:

1. Kaposi sarcoma.
2. Lymphoma.

GASTROINTESTINAL MANIFESTATIONS:[39]

DISEASES OF ORAL CAVITY:

1. Oral candidiasis.
2. Oral hairy leukoplakia.
3. Aphthous ulcers.
4. Ulcers due to cryptococcosis and histoplasmosis.

Difference between oral thrush and hairy leukoplakia:

	Oral thrush [40]	Oral hairy leukoplakia
Etiology	Candida species	EBV
Common site	Soft palate	Lateral surface of tongue
Appearance	White cheesy exudate. Erythematous borders	White frond like lesions
Treatment	Oral antifungal agents	Local podophyllin systemic antiviral agents

DISEASES OF ESOPHAGUS:

i. Esophagitis:

a. Candidiasis.

b. Cytomegalovirus esophagitis: single large ulcer.

c. Herpes simplex esophagitis: multiple small ulcers.

ii. Kaposi sarcoma.

iii. Lymphoma.

iv. Idiopathic painful ulcer: responds well to thalidomide.

INFECTIONS OF SMALL AND LARGE INTESTINE AND THEIR SPECIAL FEATURES:

Bacterial infections:

Salmonella typhimurium:

It commonly presents with non-specific symptoms.

Long term ciprofloxacin may be needed.

Salmonella typhi:

Bacteraemia is frequent.

Campylobacter jejuni:

Bloody diarrhea and proctitis are predominant features.

It responds well to erythromycin.

All the above three infections are common in homosexuals

Fungal infections:

Cryptosporidia:[41]

Their clinical spectrum ranges from self limiting diarrheal illness to fatal diarrhea.

It is confirmed by demonstrating oocysts in stool by acid fast staining.

Nitazoxanide is treatment of choice.

Prevention: Consuming uncooked shellfish must be avoided.

River or lake water must be purified before use.

Isospora belli:

Responds well to trimethoprim-sulphamethaxazole.

Microsporidia:

Enterocytozoon bieneusi is the commonest agent.

Demonstration of cyst: chromotroph based stains.

Albendazole can be tried.

Viral infections:

CMV:

It causes colitis.

It is characterized by non bloody diarrhea.

Colonoscopy: multiple mucosal ulcers.

Treatment: Ganciclovir/Foscarnet.

Apart from various opportunistic infections, HIV itself can cause malabsorption syndrome called HIV/AIDS enteropathy.

CAUSES OF RENAL FAILURE IN HIV:

HIVAN:[42]

It was initially reported only in injection drug users. So it was first named as IDU nephropathy. It is the leading cause of renal failure in PLHA. It is highly prevalent among blacks and Hispanics. Urinalysis shows microalbuminuria in early stages (in severe cases gross proteinuria). Ultrasound shows renomegaly bilaterally. Increased cortical echoes are noted. Histopathology shows focal segmental glomerulosclerosis. FSGS is of

collapsing type. Presence of HIVAN is an indication for starting antiretrovirals. Steroids and ACEI have some benefit in these patients

Drugs causing Renal failure in HIV:[43]

1. Amphotericin B.
2. Adefovir and cidofovir.
3. Foscarnet.
4. Pentamidine.
5. Cotrimoxazole: it increases serum creatinine. It competes with latter for tubular secretion.
6. Indinavir: can cause renal calculi.
7. Sulfadiazine: causes acute reversible renal injury.

For both indinavir and sulfadiazine toxicity, adequate hydration if ensured will reverse the renal injury.

SYPHILIS IN HIV:[44]

The presence of syphilis and other sexually transmitted diseases will facilitate the entry of virus as discussed earlier. Apart from usual presentations of syphilis, features which are otherwise very rare, are frequently reported in these groups.

Some of the special features of syphilis in HIV are mentioned below:

Condylomatalata: commonest presentation in HIV.

Lues maligna: Necrotizing vasculitis of skin.Present as ulcerative cutaneous lesion.

Neurosyphilis: presentation may range from meningitis to stroke and hard of hearing.

Patients may even be asymptomatic.

VDRL: false positives are common.

Anti-FTA: sometimes negative due to immunodeficiency.

Lumbar puncture: CSF analysis to rule out neurosyphilis is recommended in all cases of syphilis.

DERMATOLOGICAL DISEASES IN HIV AND THEIR SPECIAL FEATURES:[45]

Seborrheic dermatitis:

It is one of the common cutaneous manifestations. Sometimes pityrosporum are detected from the lesions.

Folliculis:

It is usually seen in individuals with CD4 less than 200.

Pruritic popular eruptions:

It is usually seen as multiple papularlesion.

Common sites are extensor surfaces, face and torso.

Eosinophilic pustular folliculitis:

It is characterised by infiltration of hair follicles with eosinophils.

Clinically they present with perifollicular papules and plaques.

Patients show elevated IgE levels.

Lesions are often associated with mites and hence may respond to topical antihelminths

Norwegian scabies:

It is the most severe form of scabies.

Pruritis is uncommon in this form.

Topical agents are of little benefit. Oral ivermectin may be preferred.

CNS DISEASE:

Toxoplasmosis:

It is the most common ICSOL among PLHA. MRI usually shows multiple ICSOLs. Basal ganglion and peripheries of the cerebrum are the common site for infection. Presence of a single ICSOL is highly unlikely in this infection, but can rarely occur. Results of serological testing are always positive. Negative result rules out the disease. Diagnosis is usually made presumptively in a patient with MRI finding and positive serology. Trial therapy can be initiated. Imaging is repeated after two weeks.

CNS lymphoma:

It is another common ICSOL among PLHA. It is a type of non-Hodgkins lymphoma. Clinically it presents like toxoplasmosis. Focal neurological deficits are common. The lesions are usually single (unlike toxoplasmosis where it is usually multiple). Biopsy confirms the diagnosis. But it should be done only in cases where ICSOL fail to resolve even after a trial with treatment for toxoplasma.

DIFFERENTIAL DIAGNOSIS FOR ICSOLs* IN HIV	
CONDITIONS	Supportive clinical features and tests
Toxoplasmosis	MRI Positive serology for Toxoplasmosis.
Primary CNS lymphoma	MRI. Stereotactic Biopsy.
Bacterial abscess	Positive blood culture recently.
Tuberculoma	Positive tuberculin tests.
Cryptococcomas	Recent fungemia.
Nocardiosis	Injection Drug users

DISEASES OF ENDOCRINE SYSTEM:

THYROID ABNORMALITIES:[45]

It is common in 10-15% of patients. Subclinical hypothyroidism is the most commonly detected thyroid abnormality among these patients.

Effects of ART on thyroid function:

1. It may result in elevated levels of TSH.
2. Immune reconstitution Graves can occur several months after initiation of therapy.

Opportunistic infections that can cause goitre:

1. Pneumocystis jiroveci.
2. Cytomegalovirus.
3. Mycobacterium.
4. Toxoplasma.
5. Cryptococcus neoformans.

LIPODYSTROPHY:[46]

It is one of the common drug related side effects seen in PLHA. Lipodystrophy is characterised by following features.

Hypertriglyceridemia	Hypercholesterolemia

Hyperglycemia	Hyperinsulinemia
Elevated apolipoprotein B	
Truncal obesity: Due to increased intraabdominal fat	
Peripheral wasting (Lipoatrophy):Noted especially in face and gluteal region	

The criteria for metabolic syndrome is met in about one fifth of these patients. Drugs to control cholesterol and triglyceride levels must be added. Agents of choice are atorvastatin and gemfibrozil as they have minimal drug interactions.

OTHER ENDOCRINE ABNORMALITIES:

Osteopenia.

Osteonecrosis.

Avascular necrosis of femur and shoulder.

Hyponatremia due to SIADH.

Hypogonadism.

Adrenal insufficiency.

DIAGNOSIS:

For diagnosis of HIV infection:

1. ELISA.
2. WESTERN BOT.
3. RAPID ANTIBODY TEST.
4. PCR

To assess the severity of infection

1. CD4 count.
2. Estimation of viral load
    a. RT-PCR
    b. bDNA assay

To facilitate treatment:

1. drug resistance testing
2. HLA typing (before initiation of abacavir)
3. Tropism testing (before starting Maraviroc)

TREATMENT:[47]

PROPHYLAXIS TO PREVENT OPPORTUNISTIC INFECTIONS:

Pneumocystis carnii:

Trimethoprim-sulphamethaxazole (one double strength tablet once a day).

In all cases where CD4 < 200.

MAC:

Azithromycin 1.2 g/week (recommended).

Clarithromycin 500 mg twice a day.

In all cases where CD4 is less than 100.

Mycobacterium tuberculosis:

Isoniazid plus pyridoxine (300+50 mg) once a day for nine to twelve months.

Recommended for all cases with positive mantoux test (more than 5mm).

Toxoplasmosis

Cotrimoxazole similar to PCP prophylaxis.In all cases with CD4 less than100.

Cytomegalovirus:

Ganciclovir 1000 mg trice a day.

In all cases where CD4 count is less than 50.

INFECTIONS FOR WHICH IMMUNIZATIONS ARE RECOMMENDED IN HIV PATIENTS

HBV	- three doses.
HAV	- two doses.
Influenza	- one dose every year.
Human papilloma virus	- recommended for age group between 9-26 years.
Streptococcal pneumonia	- recommended in all cases with CD4 more than 200.

DRUGS TO PREVENT RECURRENCES/RELAPSES

Salmonella species infection	-	Ciprofloxacin 0.5g is given twice a day for six months.
Herpes simplex infection	-	Valacyclovir 0.5 g is given twice a day.
Candida	-	Fluconazole 100-200 mg once a day.

ADJUNCTIVE MEDICATIONS

Indications for corticosteroids:

1. Severe Pneumocystis pneumonia: beneficial only if given within 3 days after diagnosis.
2. IRIS.

Epoeitin alpha:

Dose : 8000 units subcutaneous thrice a week. (Max 48000 units per week)

Target : haematocrit between 35 – 40%

Indication : PLHA with anemia with erythropoietin < 500 MU/ml

Filgrastim and sargramostin:

Indicated for cases of neutropenia

ANTIRETROVIRAL THERAPY:

ART has made a great impact in the quality of life. Now they are able to lead a healthy life like normal population. But this is not without complications. Although cART has led to increased life expectancy in HIV individuals, it has also resulted in drug related health issues which were previously uncommon. Conditions like IRIS slowly got recognised following the extensive use of drugs.

INDICATIONS FOR ART:

1. AIDS defining illness.

2. Asymptomatic individuals with following conditions:

    a. CD4 count< 500 (recommendations vary according to guidelines. NACO recommends ART when CD4 is below 300)

    b. Rapid rate of decline of CD4(>100 per year).

    c. High plasma viremia (more than one lakh copies per microliter)

    d. Pregnancy.

    e. Post exposure prophylaxis.

    f. Patients with high risk for cardiac disease and cancers.

    g. Patients with HIV related renal impairment.

    h. Serodiscordant couple (if individual has seronegative partner).

AIMS OF THERAPY:

- To improve the immune status.
- To decrease the viral load.
- To minimise drug related adverse events.
- To avoid drug resistance.

If a patient adheres to the prescribed drugs, plasma viral load should decline to undetectable levels in 3-6 months. If a patient defaults from the regimen, resistance testing must be performed before restarting ARTs.

Factors which determine agent of choice:

1. Past treatment history.
2. Resistance testing.
3. Adverse drug events.
4. Associated conditions.
5. Patient's compliance.
6. Treatment regimens and dosage.

NRTIs:

1. Zidovudine
2. Lamiudine
3. Stavudine
4. Didanosine
5. Zalcitabine
6. Emtricitabine
7. Tenofovir
8. Abacaviir

Protease inhibitors:

1. Indinavir.
2. Ritonavir.
3. Saquinavir.
4. Amprenavir.
5. Fosamprenavir.
6. Atazanavir.
7. Nelfinavir.
8. Tipranavir.
9. Darunavir.
10. Lopinavir/ritonavir.

Special properties of protease inhibitors:

Metabolism :	By liver. Through CYP450
Drug interactions:	Avoid CYP450 inducers. (rifampin)
Advantage of ritonavir boosting:	1. Decreased drug requirements. 2. Decreased adverse events.
Exceptions for boosting	1. Atazanavir. 2. Nelfinavir.
Side effects	Metabolic abnormalities: Hypertriglyceridemia. Hypercholesterolemia. Lipodystrophy.

Monitoring:	Lipid profile twice a year
Drugs to be avoided for treatment of lipodystrophy:	Simvastatin. Lovastatin.
Agents preferred:	Gemfibrozil. Atorvastatin.
Indications for gemfibrozil:	Triglyerides>500mg/dl. Dose:600mg(twice a day)

Non necleotidde reverse transcriptase inhibitors (NNRTIs):

Nevirapine

Delavirdine.

Efavirenz

Etravirine

Rilpivirine

ENTRY INHIBITORS:

1. Enfuvirtide. 2. Maraviroc.

INTEGRASE INHIBITORS:

1. Raltegravir 2. **Eltigravir:**

MATERIALS AND METHODS

Design of study	**:**	Cross sectional study
Period of study	**:**	July 2011 – September 2012
Study population	:	151 cases
Ethical clearance	**:**	Obtained
Consent	**:**	Informed consent obtained
Conflict of interest	:	Nil
Financial support	**:**	Nil.
Settings	**:**	Study was conducted in ART Centre, Government Rajaji Hospital.

Selection of study subjects:

Inclusion criteria:

Patients who were diagnosed as HIV for the first time

Exclusion criteria:

Patients who were already diagnosed as HIV positive

Patients who were previously on ART and discontinued

Children < 13 years

Study:

151 consecutive cases between the month of July and September were selected for the study after applying the inclusion and exclusion criteria as stated above and subjected to the following.

Baseline data and clinical characteristics:

The baseline characteristics of the patients were prepared. Age , sex, body weight, height, marital status, occupation, significant past history,

smoking and drinking habits, substance abuse, history regarding sexual activities, history of blood transfusion and hospitalisations were noted.

Thorough clinical examination was done in all individuals and recorded in the proforma.

HIV was tested by SD BIOLINE HIV -1/2 3.0, a rapid immunochromatographic method and later confirmed by western blot assay.

CD4 count was measured by BD FACScalibur flow cytometer.

Investigations done in all patients:

Complete hemogram including total count, differential count, haemoglobin, platelet count, ESR and peripheral smear.

Renal function tests: blood urea, serum creatine

Liver function tests: serum bilirubin, serum proteins, SGOT, SGPT, ALP.

Blood sugar

Chest x ray

Mantoux test

Sputum AFB

Fundus examination: for retinopathy

Investigations done in selected patients:

Upper GI endoscopy: for esophageal candidiasis and esophagitis due to CMV and HSV

Ultrasound abdomen: for TB abdomen

Stool for ova and cyst

VDRL: for syphilis

CT/MRI brain and CSF analysis

ECG and Lipid profile

Diagnosis of various opportunistic infections and other conditions were confirmed by concerned speciality department according to standard international guidelines. Patients were then classified based on modified WHO clinical staging of HIV/AIDS infection.

Data were entered in Microsoft Office 2007 Excel-spread sheet. Analysis performed with SPSS version 17.0 statistical package. All continuous variables were presented as mean ± standard deviation if they were normally distributed. Difference in the normally distributed variables were assessed using t test and the pair t test for dependant variable. Comparison between the two individual groups was performed using t-test. All tests were two sided and a probability value of $p<0.05$ was considered statistically significant.

RESULTS

Table – 1

Age Distribution

Age in years	No.of cases	Percentage
< 20	3	2.0
20 – 30	33	21.9
31 – 40	70	46.3
41 – 50	35	23.2
> 50	10	6.6
Total	151	100

Mean age of the study group was 36.73 (SD±8.73). Median age was 36. Of 151 cases 46.3% (70 cases) were aged between 31 to 40 years. This was followed by age group between 41-50 years (23.2%) and 21-30 years (21.9%). Out of 151 cases only three (2%) were aged below twenty years. 6.6% were aged more than 50 years. In our study 93.4% cases were below the age of fifty.

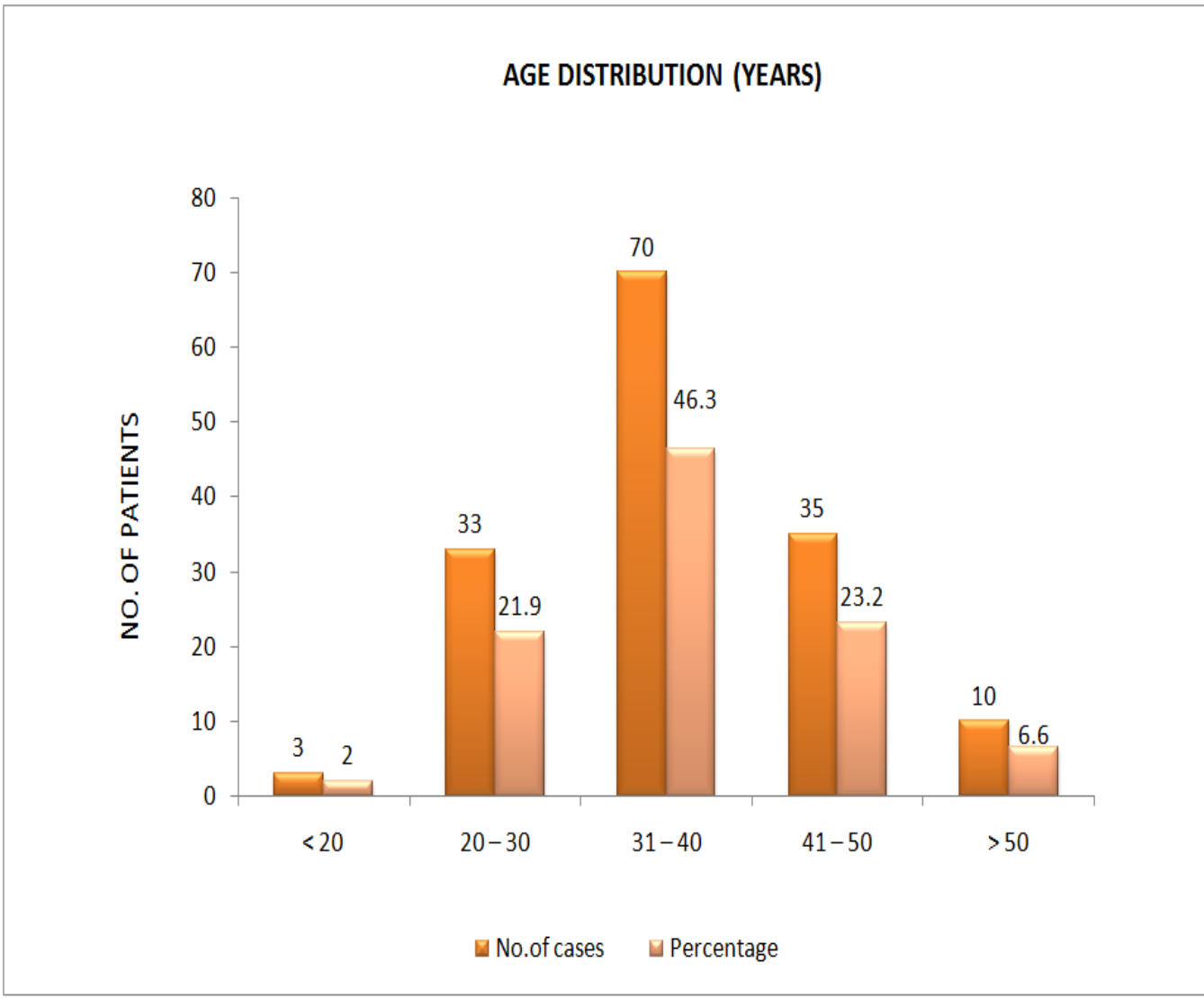

AGE DISTRIBUTION (YEARS)
NO. OF PATIENTS
80
70
60
50
40
30
20
10
0
3
2
33
21.9
70
46.3
35
23.2
10
6.6
< 20
20 – 30
31 – 40
41 – 50
> 50
No.of cases
Percentage

Table – 2

Sex Distribution

Sex	No. of cases	Percentage
Female	55	36.4
Male	96	63.6
Total	151	100

Out of 151 cases , 63.1% (96 cases)were males. Only 36.4%(55 cases) were females

Table – 3

Mode of transmission

Mode	No.of cases	Percentage
Hetero sexual	132	87.5
MSM*	3	2.0
Blood transfusion	2	1.3
Mother to child	2	1.3
Unknown	12	7.9
Total	151	100

*men having sex with men

Heterosexual mode of transmission is responsible for 87.5% (132)of cases. This was followed by MSM which was responsible for 2% of cases. Blood transfusion related transmission is responsible for 1.3% of cases. Vertical transmission from mother to child is responsible for 1.3% of cases. In 7.9% mode of transmission was not known.

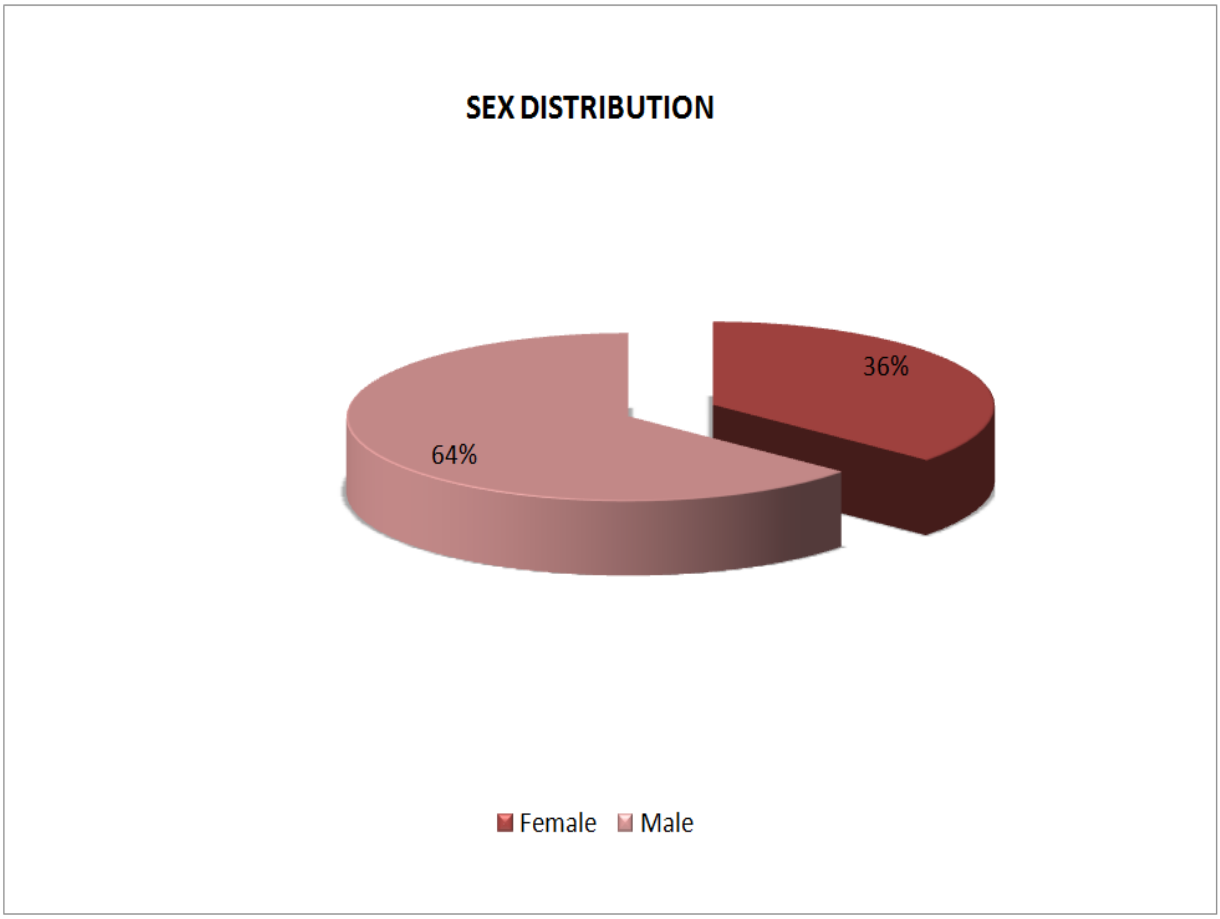

SEX DISTRIBUTION
36%
64%
Female
Male

Table – 4

Sex distribution vs Spouse positive

Sex	Total No.of HIV Positive cases	Spouse positive
Female	55	46
Male	96	41
P value	0.019 Significant	

Out of 55 females , 46 of them had HIV positive partner. Out of 96 males in our study only 41 had HIV positive partners. P value is < .019. This is statistically significant.

Table – 5

WHO Staging and distribution of cases

Stage	No.of cases	Percentage
Stage – 1	47	31.1
Stage – 2	9	5.9
Stage – 3	56	37.1
Stage – 4	39	25.9
Total	151	100

37.1% of cases who were diagnosed as HIV came under WHO stage 3. 31.1% were stage 1. Only 9 cases (5.9%) were stage 2. 25.9% of cases came under stage 4.

Table – 6

Staging Vs CD4 count

Staging	CD4 count Mean	SD
1	470.28	156.53
2	259.11	173.28
3	204.28	111.5
4	158.55	108.3

Stage 4 patients had the lowest mean CD4 count (158.55/µl) among all stages. Stage 1 had the highest mean CD4 count (470.28) when compared to other stages. Stage 2 had mean CD4 count of 259.11/µl and stage 3 had 204.28/µl.

Table – 7

Staging Vs CD4 count

Staging	Mean CD4 count	SD
Stage 4 (39)	158.5	108.3
Other stages (112)	320.3	187.34
p value	<0.001	significant

Mean CD4 count of stage 4 was 158.5/µl which was significantly low with a p value of less than 0.001 when compared to mean CD4 count of other stages which was 320.3/µl.

Table – 8

Staging Vs Sex distribution

Staging	Male	Females
1	20	27
2	1	8
3	43	13
4	32	7
Total	96	55

Table -9

Staging vs sex distribution

Staging	No of male cases	No of female cases	Total cases	p value
Stage 1 and 2	21 (22%)	35 (63.6%)	56	0.171 (not significant)
Stage 3 and 4	75 (78%)	20 (35.4%)	95	<0.001 (significant)
Total	96	55	151	

Of 55 females, 27 were stage 1, eight were stage 2, 13 were stage 3 and 7 were stage 4. Of 96 male patients, 20 cases were stage 1, one cases was stage 2, 43 cases were stage 3 and 32 cases were stage 4. Of 55 female patients, 63.6% were either asymptomatic or in stage 2. Among males 78% were either stage 3 or stage 4.

Table – 10

Staging Vs Age

Staging	Mean age	SD
1	32.47	8.24
2	38.22	9.03
3	38.95	8.57
4	38.36	7.99

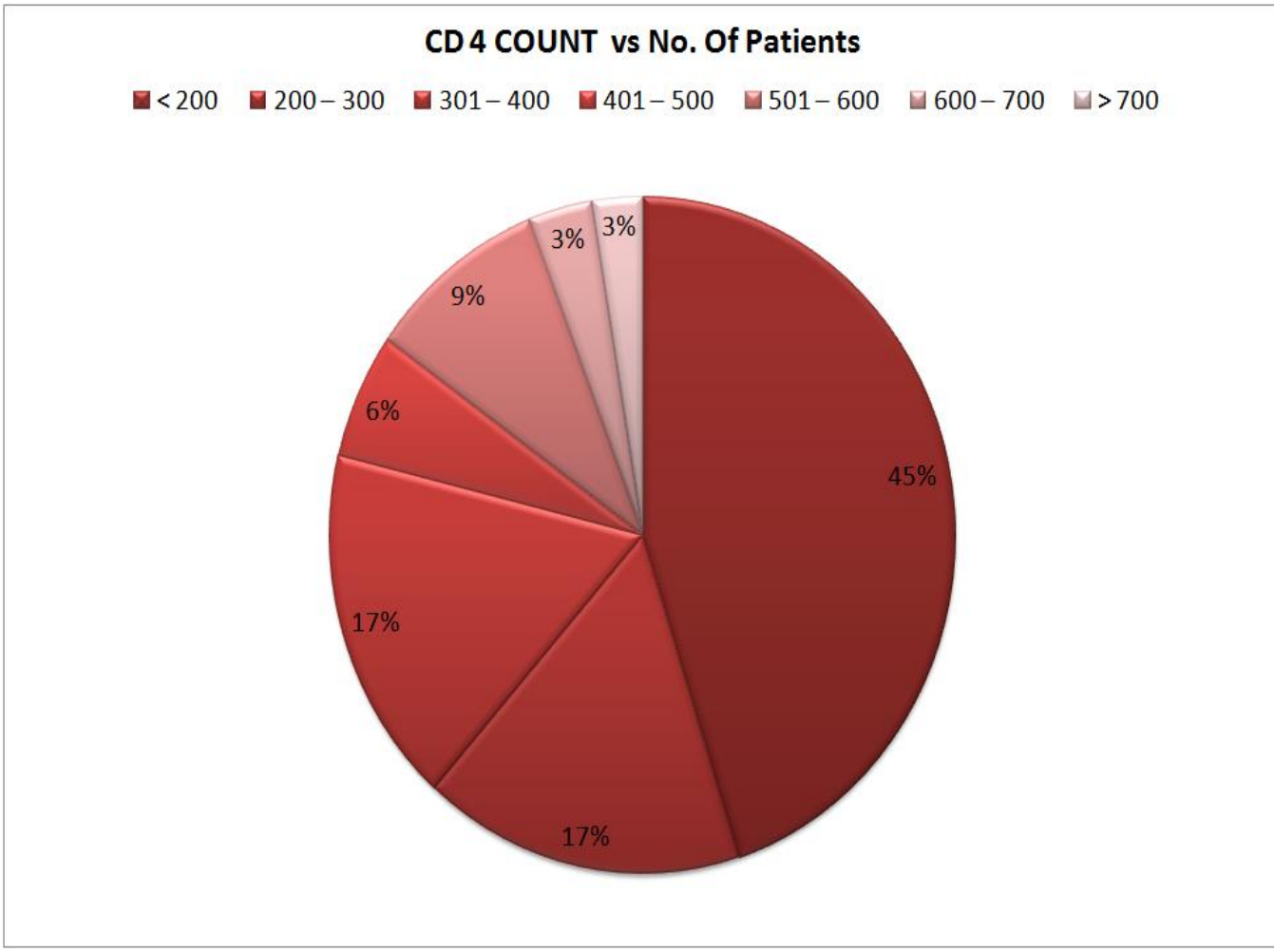
Mean age of patients who were Stage 1 was 32.47 whereas mean age of stage 3 and stage 4 were 38.95 and 38.36 respectively

Table – 11

CD4 count and distribution of patients.

CD 4 count/µl	No.of cases	Percentage
< 200	68	45.0
200 – 300	25	16.6
301 – 400	26	17.2
401 – 500	9	6.0
501 – 600	14	9.3
600 – 700	5	3.3
> 700	4	2.6
Total	151	100

25 (16.6%) cases were having CD4 below 100. 45% of the cases were having CD4 count less than 200/µl. Only 15.2% have CD4 count of more than 500/µl. Twenty five cases(16.6%) have CD4 between 200 and 300.


CD 4 COUNT vs No. Of Patients
< 200
200 – 300
301 – 400
401 – 500
501 – 600
600 – 700
> 700
45%
17%
17%
6%
9%
3%
3%

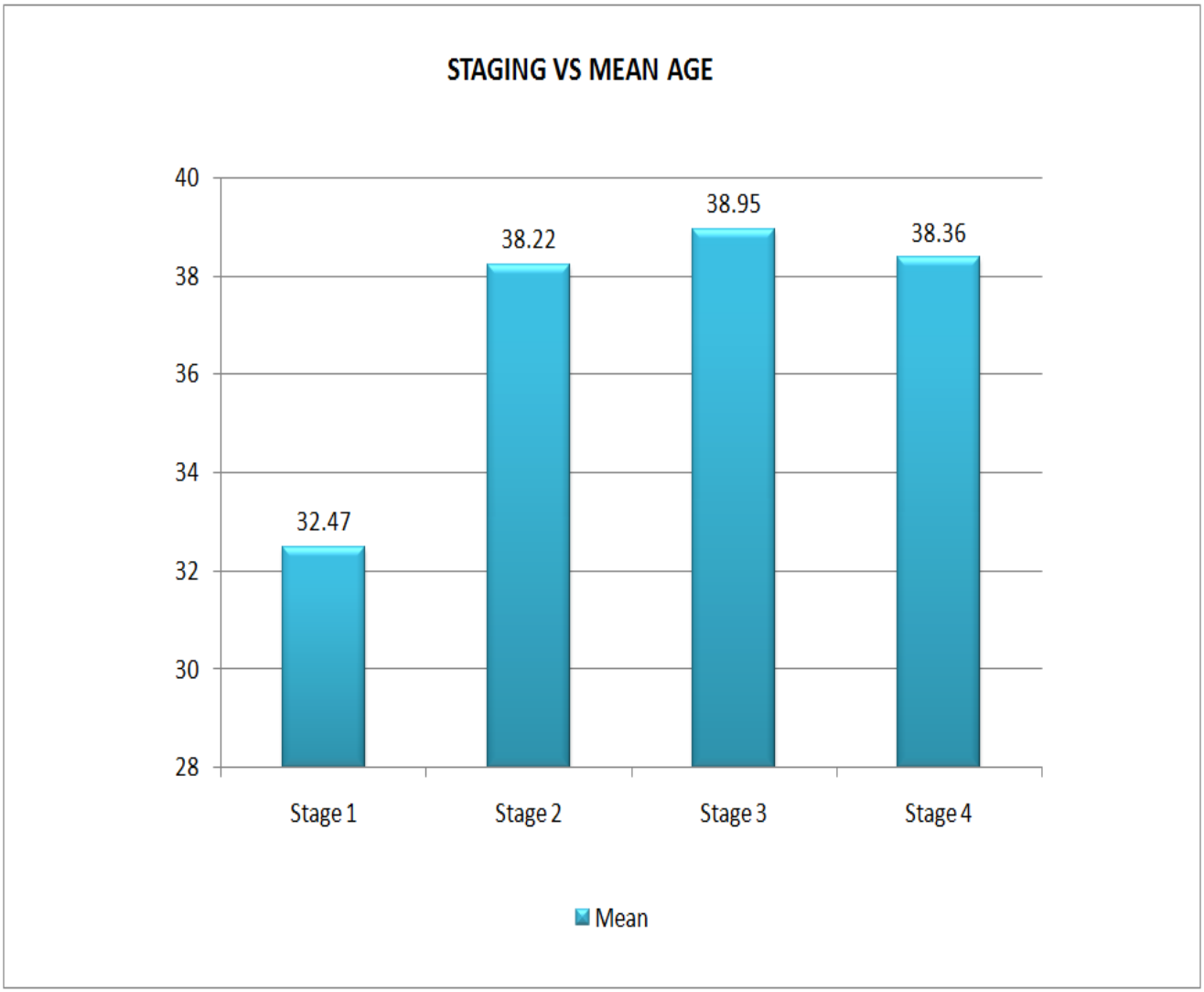

STAGING VS MEAN AGE
40
38
36
34
32
30
28
32.47
38.22
38.95
38.36
Stage 1
Stage 2
Stage 3
Stage 4
Mean

Table – 12

CD 4 count

CD 4 count	No.of cases	Percentage
< 350	107	70.9%
> 350	44	29.1%
Total	151	100
P <0.001 (significant)		

70.9% had CD4 count less than 350/µl but only 29.1% had CD4 count more than 350/µl. This was statistically significant with a p value of less than 0.001.

Table – 13

CD 4 count Vs Sex distribution

CD 4 count	Male	Female	No.of cases	P value
< 300	66	27	93	0.001 Significant
> 300	30	28	58	0.957 Not significant
Total	96	55	151	

93 cases were having CD4 less than 300/µl , of which 66 were males and 27 were females. The p value is .001 which is statistically significant

Of 58 cases who had CD4 more than 300/µl, 30 were males and 28 were asymptomatic. The p vale is .957 which is statistically not significant.

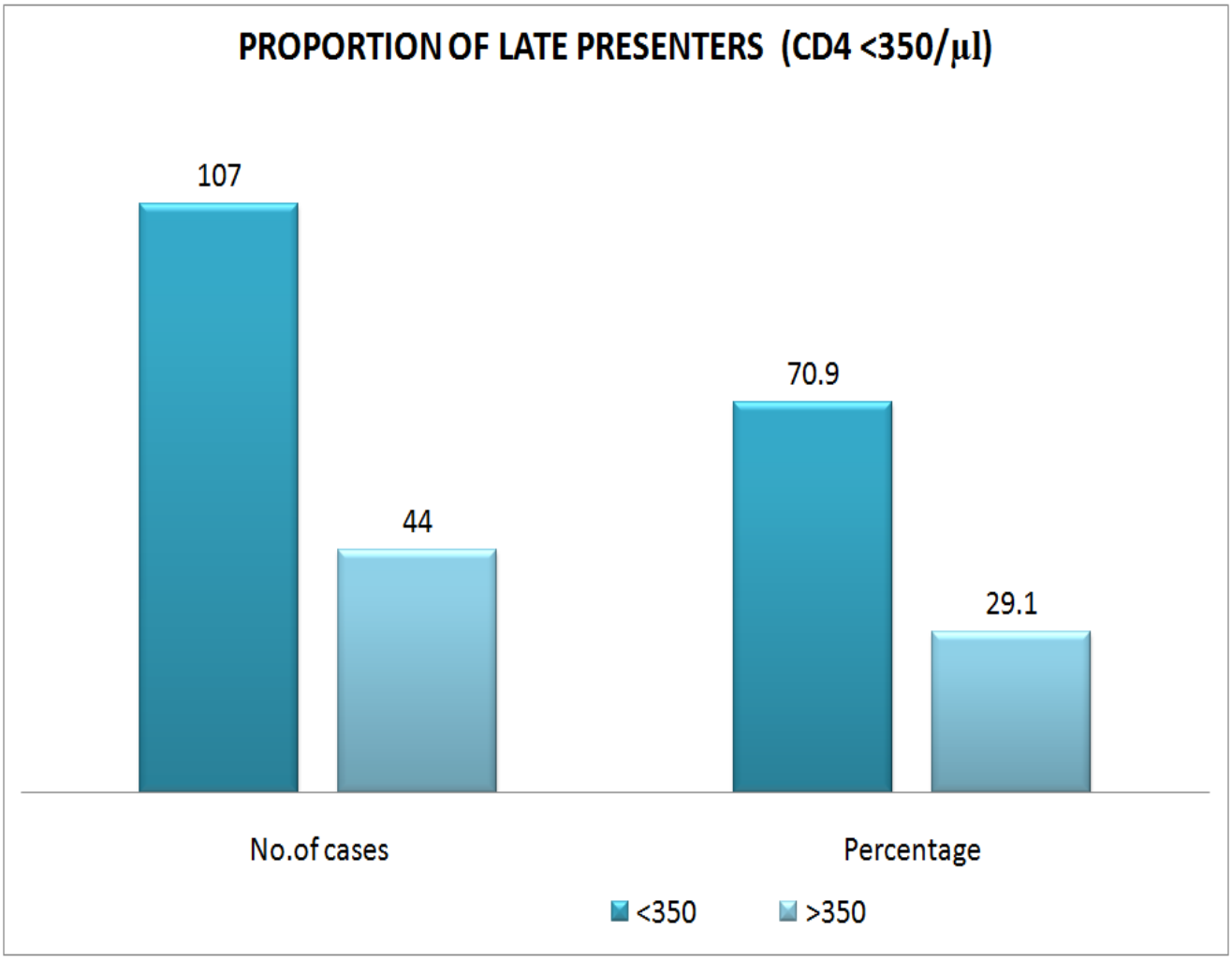

PROPORTION OF LATE PRESENTERS (CD4 <350/µl)
107
44
70.9
29.1
No.of cases
Percentage
<350
>350

Table – 14

CD4 count vs Sex Distribution

Sex	CD4 count Mean	SD
Male	259.1	183.5
Female	312.4	182.5
P value	0.087 Not significant	

Overall mean CD4 count of all patients in our study were 278.5/µl (SD ±184.37)Mean CD4 count of males were 259.1/µl. The mean CD4 count of females were 312.4/µl which was little higher than males.CD4 counts in males were not significantly lower than those of females (p value of 0.087)

Table – 15

Presenting manifestations in newly diagnosed HIV patients

	No.of cases	Percentage
Asymptomatic	**47**	**31.1**
Symptomatic	**104**	**68.9**

COMMON CLINICAL Percentage

CONDITIONS	(no of cases)
Oral Candidiasis	32.45% (49)
Unexplained chronic Diarrhea	27.15% (41)
Unexplained Severe Weight Loss	23.84% (36)
Unexplained Persistent Fever	18.54% (28)
Pulmonary Tuberculosis	17.22% (26)
Moderate Unexplained Weight Loss	13.25% (20)
Oral Hairy Leukoplakia	4.64% (7)
Severe Bacterial Infections	3.97% (6)
Herpes Zoster	3.31% (5)
Esophageal Candidiasis	1.32% (2)
Recurrent Severe Bacterial Pnuemonia	0.66% (1)
Cryptococcal Meningitis	0.66% (1)
Invasive Cervical Carcinoma	0.66% (1)
Symptomatic Cardiomyopathy	0.66% (1)

OTHER UNCOMMON CONDITIONS:

Extrapulmonary Tuberculosis

Peripheral Neuropathy

Seborrheic Dermatitis

RARE CLINICAL CONDITIONS:

Of the 151 cases, 104 patients are symptomatic. They have varied presentations. Also same patient had multiple clinical manifestations.

The commonest presentation in our study was oral candidiasis which was present in 32.45% (49) of cases. This was followed by unexplained severe diarrhea which was present in 27.15% of cases. Unexplained severe weight loss (more than 10 kg) was the third most common presentation (23.84%). If both moderate and severe weight loss were considered together,

weight loss was present in more number of cases than oral candidiasis. Unexplained fever for more than thirty days was present in 18.58 % of cases. Pulmonary tuberculosis was the second most common opportunistic infection next only to oral candidiasis. PCP pneumonia was present in twenty cases (13.25%)

PROPORTION OF PATIENTS (%) WITH VARIOUS CLINICAL MANIFESTATIONS
35
30
25
20
15
10
5
0
32.45
31.1
27.15
23.84
18.54
17.22
13.25
13.25
7.95
7.95
7.28
4.64
3.97
3.31
1.32
1.32
0.66
0.66
0.66
Other Circumstances
Asymptomatic
Unexplained Chronic Diarrhea
Unexplained Severe Weight Loss
Unexplained Persistent Fever
Pulmonary Tuberculosis
Moderate Unexplained Weight Loss
PCP Pnuemonia
Lymphadenopathy
Extrapulmonary Tuberculosis
Angular Cheilitis
Oral Hairy Leucoplakia
Seborrheic Dermatitis
Herpes Zoster
Severe Bacterial Infections
Esophageal Candidiasis
Recurrent Severe Bacterial Pnuemonia
Cryptococcal Meningitis
Invasive Cervical Carcinoma

Other uncommon conditions were lymphadenopthy (7.95%), extrapulmonary tuberculosis (7.95%), angular cheilitis (7.28%), oral hairy leukoplakia (4.64 %), seborrheic dermatitis (3.97 %) and herpes zoster (3.31%)

Two cases of severe bacterial infections were diagnosed to be HIV. One of them had pulmonary abscess and the other had submandibular abscess. Two patients had esophageal candidiasis. Recurrent bacterial pneumonia, cryptococcal meningitis, invasive cervical carcinoma and dilated cardiomyopathy were present in one patient each.

Table – 16

Other circumstances for HIV screening

Reason for screening	No.of cases
Spouse screening*	29 (19.2)
Voluntary screening#	12 (7.9)
Preoperative screening*	3 (2.0)
Child screening*	2 (1.3)
Antenatal screening*	1 (0.7)
Total	47 (31.1%)

* provider initiated clients

general clients from public. (client initiated clients)

Out of 151 cases, 47 (31%) patients were asymptomatic. 29 (19.2%) of them were screened because of having a HIV positive partner. Twelve individuals were found out to be positive after voluntary screening. Three cases were found out to be positive during preoperative assessment. Two cases of mother to child transmission were noted. One case was diagnosed during antenatal visit.

Table – 17

CD4 Count Vs Oral candidiasis

CD4 COUNT	No.of cases	Oral Candidiasis
< 200	68	40
> 200	83	9
P value	< 0.001 Significant	

Out of 151 cases 49 had oral candidiasis. 40 of them had CD4 count of less than 200/µl. There was significant relationship between oral candidiasis and CD4 count less than 200/µl, with a p value of less than 0.001.

Table – 18

CD4 Count Vs Pulmonary tuberculosis

CD4 COUNT	No.of cases	Pulmonary tuberculosis
< 200	68	18
> 200	83	8
P value	0.039 Significant	

Out of 151 cases 26 had pulmonary tuberculosis. 18 of them had CD4 count of less than 200/µl. There was significant relationship between pulmonary tuberculosis and CD4 count less than 200/µl, with a p value of 0.039.

Table – 19

CD4 Count Vs Extra pulmonary tuberculosis

CD4 COUNT	No.of cases	Extra pulmonary tuberculosis
< 200	68	10
> 200	83	2
P value	0.024 Significant	

Table-20

Tuberculosis involving various organs

System	Percentage (No. Of cases)
Pulmonary tuberculosis	68.4 (26)
Tuberculous meningitis	18.4 (7)
Tuberculous lymph node	11 (4)
TB abdomen	2.6 (1)
Total no of cases	100 (38)

Out of 151 cases 12 had extrapulmonary tuberculosis. 10 of them had CD4 count of less than 200/µl. There was significant relationship between extrapulmonary tuberculosis and CD4 count less than 200/µl, with a p value of 0.024. Tuberculous meningitis was the most common extrapulmonary tuberculosis followed by TB lymph node and TB abdomen.

Table – 21

CD4 Count Vs PCP pneumonia

CD4 COUNT	No.of cases	PCP pneumonia
< 200	68	17
> 200	83	3
P value	0.002 Significant	

Out of 151 cases 20 had PCP pneumonia. 17 of them had CD4 count of less than 200/µl. There was significant relationship between PCP pneumonia and CD4 count less than 200/µl, with a p value of 0.002.

Table – 22

CD4 Count Vs Weight Loss

CD4 COUNT	No.of cases	Weight loss
< 200	68	42
> 200	83	14
P value	< 0.001 significant	

Out of 151 HIV cases, 64 had weight loss. Among them 42 patients had CD4 count less than 200/µl.There was significant relationship between weight loss and CD4 count less than 200/µl, with a p value of less than 0.001.

DISCUSSION

AGE PROFILE:

In our study 93.4% cases were of age below fifty years and majority of them (46.3%) were between 31 to 40 years. This may be because of delay in diagnosing HIV in these patients. This was proven by the fact that mean age of Stage 1 was 32 years whereas for other stages it was around 38 years. In a study by Kumar et al [50], the mean age was thirty five years and significant proportion were presented with low CD4 levels (median 187/µl). Hence IEC and HIV/AIDS awareness campaigns should target younger age groups so that HIV can be diagnosed at earlier asymptomatic stage itself.

GENDER PROFILE:

Males (63.6%) occupy greater proportion of our study group. Also 78% of males present in either stage 3 or 4 i.e. in advanced stages. CD4 count of males (259.1) were much lower than the female (312.4) counterpart but it was not statistically significant. But male sex had statistically significant association ($p<0.001$) with CD4 count of less than 300/µl. Also it was noted that 78% of males present in either stage 3 or stage 4.

Female sex in our study have low incidence (35.4%) for HIV. This was correlating with our national statistics in which HIV prevalence in females were thirty nine percent [7]. In addition 63.6% of females were in either asymptomatic stage or stage 2. A study by Newmann et al [51] in South India showed that about 50% of newly diagnosed females were asymptomatic. It also showed that about eighty one percent were married and ninety percent

were monogamous in sex. In our study 46 out of 55 (83.6%) females were having HIV positive partner. In contrast only 41 out of 96 males (42.7%) were having HIV positive partners. There was statistically significant association between female sex and presence of HIV positive partner. Our study indicates that male sex is predominantly responsible for transmitting the infection (to married women). Also it indicates the polygamous nature of male sex and necessity for intense awareness campaign regarding protective sex among the high risk male population (migrant workers, truck drivers, clients of sex workers) [7]

MODE OF TRANSMISSION:

The commonest mode of transmission in our study was heterosexual route which is the predominant mode of transmission in India. In our study there were no cases reported among injection drug abusers. This may be because of the culture of the population studied which is predominantly from rural regions around Madurai. Injection drug users are uncommon in rural areas whereas it is quite common in urban regions. IDUs form significant proportion of HIV population only in north eastern states of India.[52]

CLINICAL PROFILE:

Among 151 cases, 104 were symptomatic. In our study oral candidiasis was the commonest opportunistic infection (32.45%) among HIV cases. This

was followed by pulmonary tuberculosis (17.22%). This was followed by PCP pneumonia.

Besides pulmonary tuberculosis, extrapulmonary tuberculosis (7.95%) was also commonly seen. Tuberculous meningitis was the most common form of extrapulmonary tuberculosis which was followed by TB lymph node and TB abdomen.

Around sixty percent of AIDS patients in India are having tuberculosis.[53] Many Indian studies have shown that tuberculosis and candidiasis are the commonest OIs presenting in newly diagnosed HIV patients. [50][54]

High incidence of tuberculosis in newly diagnosed HIV patients is also due to close coordination of HIV (NACP) and TB (RNTCP) programs in India. All newly diagnosed HIV patients were screened for tuberculosis during the initial evaluation (intensified TB case finding) and vice versa i.e., all newly diagnosed tuberculosis are screened for HIV. In India as per 2010 estimates, about 3.28 lakh HIV patients were diagnosed to have tuberculosis and twenty one thousand TB patients were found out to be HIV reactive.[53]

Opportunistic infections and diseases involving oral cavity and skin were present in significant proportion of cases. Oral candidiasis was present in 32.45%, angular cheilitis in 7.28%, oral hairy leukoplakia in 4.64%, seborrheic dermatitis in 3.97%, herpes zoster in 3.31% of cases. As suggested

by Garmen et al, these manifestations can provide a potential clue to the underlying immunocompromised state.[55]

Cryptococcol meningitis is the commonest cause of meningitis among PLHA. But in our study only one case was reported. This may be because of the fact that this infection occurs only at very low CD4 levels (<100) and in our study group only twenty five cases (16.6%) were having CD4 of below 100. [56][[57]

ASYMPTOMATIC GROUP:

31.1% cases of our study were asymptomatic. Partner screening contributes to 19.2% of all cases. Out of 154 cases only twelve (7.9%) were client initiated clients. Seropositivity rate by client driven voluntary testing is very low in Tamilnadu (1.69%) when compared to Manipur (7.77%). [7] Campaigning to encourage voluntary testing is an important strategic measure for control of HIV/AIDS. Granich et al from Switzerland had proposed a mathematical model, [58] stating that implementation of universal voluntary testing and initiating ART can make a major impact on HIV pandemic. If proportion of individuals diagnosed by voluntary testing increases, it would definitely lead to rise in mean CD4 count and number of asymptomatic patients at the time of initial presentation. Early diagnosis can also prevent transmission to at risk serodiscordant partners.

IMMUNOLOGICAL PROFILE:

In our study mean CD4 count in newly diagnosed HIV patients was 278.5/µl. Mean CD4 count in male was 259.1/µl and in female was 312.4/µl. CD4 counts in males were not significantly lower than those of females (p value of 0.087). But 78% of males presented in either stage 3 or stage 4 (p value <0.001).

CD4 count decreases as stage advances. Mean CD4 count of stage 4 disease was 158 which was very low (p value of less than 0.001) when compared to rest of the stages. Mean CD4 count of stage 1 was 470.28/µl. Newer treatment guidelines recommend initiation of ART at CD4 count of 500/µl. [48] But most Indian studies show that mean CD4 count at the time of diagnosis were very low.[50][54]

Also our study showed that there was a statistically significant association between low CD4 levels (<200) and risk of opportunistic infections like oral candidiasis (p <0.001), pulmonary (p value 0.039) and extrapulmonary tuberculosis (p vale 0.024) and PCP pneumonia (p <0.002). Risk of opportunistic infections increases with declining CD4 levels.

LATE PRESENTERS:

Antinori et al has put forward definition of late presenters. [59] This has been implemented worldwide. The definition includes two groups. 1. Those with CD4 of less than 350. 2) Those presenting with AIDS defining illness. In

our study 70.9% presented with CD4 less than 350 and 25.9% patients presented with AIDS.

Study by Michael. CG et al [60] showed that CD4 count at the time of initiation of ART has significant impact on immunological recovery, with high levels of CD4 count being associated with good response to therapy. Late presenters not only have poorer quality of life but they also create huge economic burden for the country. Financial impact due to delayed diagnosis has been stressed in several studies. The cost of medical care in patents presenting at late stages is 200% higher than those who were diagnosed earlier.[61][62] This has been primarily attributed to frequent opportunistic infections and hospitalisations in the former group.

SUMMARY

1. Mean age of the study group was 36.73
2. Males are predominantly involved.
3. Most of the females were married and have HIV positive partners.
4. Most of the males present in either stage 3 or stage 4
5. Heterosexual route was the predominant mode of transmission.

6. Oral candidiasis and tuberculosis were the commonest opportunistic infections.
7. Weight loss, chronic diarrhea and fever of unknown origin were commonest non specific symptoms.
8. Tuberculous meningitis was the commonest extrapulmonary tuberculosis.
9. Mean age of Stage 1 was low when compared to other stages.
10. Mean CD4 count in our study was 278.5. For males: 259.1. For females: 312.4
11. CD4 count of stage 4 was statistically lower than other stages.
12. Oral candidiasis, tuberculosis and PCP pneumonia correlate significantly with CD4 count less than 200

CONCLUSION

Proportion of late presenters are very high worldwide. Early diagnosis in these patients would have helped them to survive for longer periods. Recommendations must be made to integrate HIV testing along with basic investigations during routine health visits in high risk individuals. Awareness

must be created among serodiscordant couples and HIV infected partner may be advised to start on ART to reduce the transmission to HIV negative partner.

Awareness about the availability of voluntary testing must be created among high risk individuals as well as general population.

The immense knowledge and scientific advances in the field of HIV/AIDS would become meaningless if the available valuable resources underutilized by the community. So the special focus should be made to diagnose the HIV patients at early stages to achieve WHOs ambitious target of zero "AIDS related death".

ABBREVIATIONS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
PLHA	People Living With HIV and AIDS
Cart	Combined Antiretroviral Therapy
PCP	Pneumocystis carrnii Pneumonia
NRTI	Nucleoside Reverse Transcriptase Inhibitor

NNRTI	Non-neucleoside Reverse Transcriptase Inhibitors
OIs	Opportunistic Infections
FDA	Food and Drug Administration
CDC	Centre for Disease Control
WHO	World Health Organisation
ELISA	Enzyme Linked Immunosorbent Assay
HTLV	Human T-Lymphotropic Virus
CD4	Cluster of Differentiation 4
MHC	Major Histocompatibility Complex
CRF	Circulating Recombinant Forms
NACO	National AIDS Control Organisation
HIVAN	HIV associated Nephrropathy
CMV	Cytomegalovirus
ICSOL	Intracranial space occupying lesions

BIBLIOGRAPHY

1.. Sharp, P. M.; Bailes, E.; Chaudhuri, R. R.; Rodenburg, C. M.; Santiago, M. O.; Hahn, B. H. (2001). "the origins of acquired immune deficiency syndrome viruses:where and when?" Philosophical Transactions of the Royal Society B: Biological Sciences 356: 867–76.

2. Worobey, M., Gemmel, M., Teuwen, D. E., Haselkorn, T., Kunstman, K., Bunce, M., ... & Wolinsky, S. M. (2008). Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature, 455(7213), 661-664.

3. Gottlieb, M. S. (2006). Pneumocystis pneumonia—Los Angeles. American Journal of Public Health, 96(6), 980.
4. Gottlieb, Michael S., R. Schroff, S. Fligiel, J. L. Fahey, and A. Saxon. "Gay-related immunodeficiency (GRID) syndrome: Clinical and autopsy observations." Clinical Research 30 (1982): 349A.
5. Blattner, W. A. (1991). HIV epidemiology: past, present, and future. The FASEB journal, 5(10), 2340-2348.
6. US GLOBAL HEALTH POLICY: THE GLOBAL HIV/AIDS FACT SHEET NOV 2012. www.kff.org/hivaids/upload/3030-17.pdf
7. National AIDS control organisation. Ministry of health and family welfare, Government of India. Annual report 2010-2011 www.nacoonline.org/upload/REPORTS/NACO%20Annual%20Report%202010-11.pdf
8. Cullen, B. R. (1991). Human immunodeficiency virus as a prototypic complex retrovirus. Journal of virology, 65(3), 1053.
9. Jawetz, Melnick, & Adelberg's Medical Microbiology, Twenty-Fourth Edition Copyright © 2007 by The McGraw-Hill Companies, Inc. Chapter 44: AIDS and lentivirus.
10. Frankel, A. D., & Young, J. A. (1998). HIV-1: fifteen proteins and an RNA. Annual review of biochemistry, 67(1), 1-25.
11. Robertson, D. L., J. P. Anderson, J. A. Bradac, J. K. Carr, B. Foley, R. K. Funkhouser, F. Gao et al. "HIV-1 nomenclature proposal." Science 288, no. 5463 (2000): 55-55.
12. Osmanov, S., Pattou, C., Walker, N., Schwardländer, B., & Esparza, J. (2002). Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. JAIDS Journal of Acquired Immune Deficiency Syndromes, 29(2), 184-190.
13. Taylor, Barbara S., Magdalena E. Sobieszczyk, Francine E. McCutchan, and Scott M. Hammer. "The challenge of HIV-1 subtype diversity." New England Journal of Medicine 358, no. 15 (2008): 1590-1602.

14. Geijtenbeek, T. B., Kwon, D. S., Torensma, R., van Vliet, S. J., van Duijnhoven, G. C., Middel, J., ... & van Kooyk, Y. (2000). DC-SIGN, a Dendritic Cell–Specific HIV-1-Binding Protein that Enhances< i> trans</i>-Infection of T Cells. cell, 100(5), 587-597.
15. Chun, T. W., Engel, D., Berrey, M. M., Shea, T., Corey, L., & Fauci, A. S. (1998). Early establishment of a pool of latently infected, resting CD4+ T cells during primary HIV-1 infection. Proceedings of the National Academy of Sciences, 95(15), 8869-8873.
16. Strizki, J. (2008). Targeting HIV attachment and entry for therapy. Advances in Pharmacology, 56, 93-120.
17. Keele, B. F., Giorgi, E. E., Salazar-Gonzalez, J. F., Decker, J. M., Pham, K. T., Salazar, M. G., ... & Shaw, G. M. (2008). Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. Proceedings of the National Academy of Sciences, 105(21), 7552-7557.
18. Kirchhoff, F. (2010). Immune evasion and counteraction of restriction factors by HIV-1 and other primate lentiviruses. Cell host & microbe, 8(1), 55-67.
19. Mangeat, B., Turelli, P., Caron, G., Friedli, M., Perrin, L., & Trono, D. (2003). Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. Nature, 424(6944), 99-103.
20. Stremlau, M., Owens, C. M., Perron, M. J., Kiessling, M., Autissier, P., & Sodroski, J. (2004). The cytoplasmic body component TRIM5α restricts HIV-1 infection in Old World monkeys. Nature, 427(6977), 848-853.
21. Neil, S. J., Zang, T., & Bieniasz, P. D. (2008). Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. Nature, 451(7177), 425-430.
22. Szabo, R., & Short, R. V. (2000). How does male circumcision protect against HIV infection?. BMJ: British Medical Journal, 320(7249), 1592.

23. Stringer, E. M., Levy, J., Sinkala, M., Chi, B. H., Matongo, I., Chintu, N., & Stringer, J. S. (2009). HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial. Aids, 23(11), 1377-1382.
24. Kroner, B. L., Rosenberg, P. S., Aledort, L. M., Alvord, W. G., & Goedert, J. J. (1994). HIV-1 infection incidence among persons with hemophilia in the United States and western Europe, 1978-1990. Multicenter Hemophilia Cohort Study. Journal of acquired immune deficiency syndromes, 7(3), 279.
25. Simonds, R. J., Holmberg, S. D., Hurwitz, R. L., Coleman, T. R., Bottenfield, S., Conley, L. J., ... & Rogers, M. F. (1992). Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. New England Journal of Medicine, 326(11), 726-732.
26. De Cock, K. M., Fowler, M. G., Mercier, E., de Vincenzi, I., Saba, J., Hoff, E., & Shaffer, N. (2000). Prevention of mother-to-child HIV transmission in resource-poor countries. JAMA: the journal of the American Medical Association, 283(9), 1175-1182.
27. MacNeal, R. J. D. J. G., & Dinulos, J. G. (2006). Acute retroviral syndrome. Dermatologic clinics, 24(4), 431-438.
28. Dorrucci, M., Rezza, G., Vlahov, D., Pezzotti, P., Sinicco, A., Nicolosi, A., ... & Pristerà, R. (1995). Clinical characteristics and prognostic value of acute retroviral syndrome among injecting drug users. Italian Seroconversion Study. AIDS (London, England), 9(6), 597.
29. Mogensen, T. H., Marinovskij, E., & Larsen, C. S. (2007). Acute demyelinizating encephalomyelitis (ADEM) as initial presentation of primary HIV infection. Scandinavian journal of infectious diseases, 39(6-7), 630-634.
30. Miedema, F., Petit, A. J., Terpstra, F. G., Schattenkerk, J. K., De Wolf, F., Al, B. J., ... & Goudsmit, J. (1988). Immunological abnormalities in human immunodeficiency virus (HIV)-infected asymptomatic homosexual men. HIV affects the immune system before CD4+ T helper cell depletion occurs. Journal of Clinical Investigation, 82(6), 1908.

31. CLERICI, M., BALOTTA, C., MERONI, L., FERRARIO, E., RIVA, C., TRABATTONI, D., ... & GALLI, M. (1996). Type 1 cytokine production and low prevalence of viral isolation correlate with long-term nonprogression in HIV infection. AIDS research and human retroviruses, 12(11), 1053-1061.
32. Pereyra, F., Palmer, S., Miura, T., Block, B. L., Wiegand, A., Rothchild, A. C., & Walker, B. D. (2009). Persistent low-level viremia in HIV-1 elite controllers and relationship to immunologic parameters. Journal of Infectious Diseases, 200(6), 984-990.
33. World Health Organisation: Interim WHO Clinical staging of HIV/AIDS And HI/AIDS case definitions for Surveillance www.who.int */hiv/pub /guidelines/ clinicalstaging.pdf*
34. Miller, R. (1996). HIV-associated respiratory diseases. Lancet, 348(9023), 307.
35. Catherinot, E., Lanternier, F., Bougnoux, M. E., Lecuit, M., Couderc, L. J., & Lortholary, O. (2010). Pneumocystis jirovecii pneumonia. Infectious disease clinics of North America, 24(1), 107-138.
36. Goletti, D., Weissman, D., Jackson, R. W., Graham, N. M., Vlahov, D., Klein, R. S., ... & Fauci, A. S. (1996). Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. The journal of Immunology, 157(3), 1271-1278.
37. Jones, B. E., Young, S. M., Antoniskis, D., Davidson, P. T., Kramer, F., & Barnes, P. F. (1993). Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. American Journal of Respiratory and Critical Care Medicine, 148(5), 1292-1297.
38. WHO | The **Three** I's for **HIV/TB** *www.who.int/hiv/topics/tb/3is/en/*
39. Sharpstone, D., & Gazzard, B. (1996). Gastrointestinal manifestations of HIV infection. The Lancet, 348(9024), 379-383.

40. Samaranayake, L. P., & Holmstrup, P. (2006). Oral candidiasis and human immunodeficiency virus infection. Journal of Oral Pathology & Medicine, 18(10), 554-564.
41. Blanshard, C., Jackson, A. M., Shanson, D. C., Francis, N., & Gazzard, B. G. (1992). Cryptosporidiosis in HIV-seropositive patients. QJM, 85(2-3), 813-823.
42. Ross, M. J., & Klotman, P. E. (2004). HIV-associated nephropathy. Aids, 18(8), 1089-1099.
43. Wyatt, C. M., Arons, R. R., Klotman, P. E., & Klotman, M. E. (2006). Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. Aids, 20(4), 561-565.
44. Rompalo, A. M., Joesoef, M. R., O'DONNELL, J. A., Augenbraun, M., Brady, W., Radolf, J. D., ... & Rolfs, R. T. (2001). Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. Sexually transmitted diseases, 28(3), 158-165.
45. Kumarasamy, N., Solomon, S., Madhivanan, P., Ravikumar, B., Thyagarajan, S. P., & Yesudian, P. (2001). Dermatologic manifestations among human immunodeficiency virus patients in south India. International journal of dermatology, 39(3), 192-195.
46. Mayer, K. H., Hoffmann, C. J., & Brown, T. T. (2007). Thyroid function abnormalities in HIV-infected patients. Clinical infectious diseases, 45(4), 488-494.
47. Carr, A. (2003). HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. Aids, 17, S141-S148.
48. Current Medical Diagnosis and Treatmen 2013 *books.google.co.in /books?isbn=0071781838*
49. Roehr, B. (2009). Should men who have ever had sex with men be allowed to give blood? Yes. BMJ, 338, b311
50. Kumar, S., Wanchu, A., Abeygunasekera, N., Sharma, A., Singh, S., & Varma, S. (2012). Profile of presentation of Human Immunodeficiency

Virus infection in North India, 2003-2007. *Indian Journal of Community Medicine*, *37*(3), 158.

51. Newmann, S., Sarin, P., Kumarasamy, N., Amalraj, E., Rogers, M., Madhivanan, P., ... & Solomon, S. (2000). Marriage, monogamy and HIV: a profile of HIV-infected women in south India. International journal of STD & AIDS, 11(4), 250-253.

52. Sarkar, S., Das, N., Panda, S., Naik, T. N., Sarkar, K., Singh, B. C., ... & Tripathy, S. P. (1993). Rapid spread of HIV among injecting drug users in north-eastern states of India. Bull Narc, 45(1), 91-105.

53. TB HIV Module For ART Centre Staff: National AIDS Control Organisation And Central TB Division, Ministry Of Health And Family Welfare , Government Of India. http://www.tbcindia.nic.in/pdfs/TB-HIV%20Module%20for%20ART%20Centre%20Staff.pdf

54. Ghate, M. V., Mehendale, S. M., Mahajan, B. A., Yadav, R., Brahme, R. G., Divekar, A. D., & Paranjape, R. S. (2000). Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. National Medical Journal of India, 13(4), 183-187.

55. Garman, M. E., & Tyring, S. K. (2002). The cutaneous manisfestations of HIV infection. Dermatologic clinics, 20(2), 193-208.

56. Pinner, R. W., Hajjeh, R. A., & Powderly, W. G. (1995). Prospects for preventing cryptococcosis in persons infected with human immunodeficiency virus. Clinical infectious diseases, 21(Supplement 1), S103-S107.

57. Park, B. J., Wannemuehler, K. A., Marston, B. J., Govender, N., Pappas, P. G., & Chiller, T. M. (2009). Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. Aids, 23(4), 525-530.

58. Granich, R. M., Gilks, C. F., Dye, C., De Cock, K. M., & Williams, B. G. (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. The Lancet, 373(9657), 48-57.

59. Antinori, A., Coenen, T., Costagiola, D., Dedes, N., Ellefson, M., Gatell, J., ... & De Wolf, F. (2010). Late presentation of HIV infection: a consensus definition. HIV medicine, 12(1), 61-64.

60. Michael, C. G., Kirk, O., Mathiesen, L., & Nielsen, S. D. (2002). The naive CD4+ count in HIV-1-infected patients at time of initiation of highly active antiretroviral therapy is strongly associated with the level of immunological recovery. Scandinavian journal of infectious diseases, 34(1), 45-49.

61. Krentz, H. B., & Gill, M. J. (2012). The direct medical costs of late presentation (< 350/mm3) of HIV infection over a 15-year period. AIDS research and treatment, 2012.

62. Krentz, H. B., Auld, M. C., & Gill, M. J. (2004). The high cost of medical care for patients who present late (CD4< 200 cells/μL) with HIV infection. HIV medicine, 5(2), 93-98.

PROFORMA

NAME AGE/SEX:

ADDRESS

REFERRAL DEPARTMENT

PRESENTING SYMPTOMS:

PAST HX: TREATMENT HX:

SMOKER:Y/N ALCOHOLIC:Y/N DRUG ABUSE:Y/N

MARITAL STATUS

SEXUAL HABITS:

CLINICAL FINDINGS:

WEIGHT: HEIGHT:

TC: DC: HB: CHEST X RAY:

ESR: MANTOUX: SPUTUM AFB:

BL. SUGAR: UREA: CREATININE: LFT:

FUNDUS VDRL:

OTHER SPECIAL INVESTIGATIONS:

CD4 COUNT:

DIAGNOSIS: SPECIALIST OPINION:

OPPORTUNISTIC INFECTIONS:

WHO CLINICAL STAGING:

Ref. No. 5336 /E4/3/2012 Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
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Govt Rajaji Hospital, Madurai 625020.
Convenor
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Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

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1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
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11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr. Rajasekar. N	M.D Gen med	Clinical and immunologic profile in individuals with newly diagnosed HIV infection.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.

She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.

4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

17.8.12

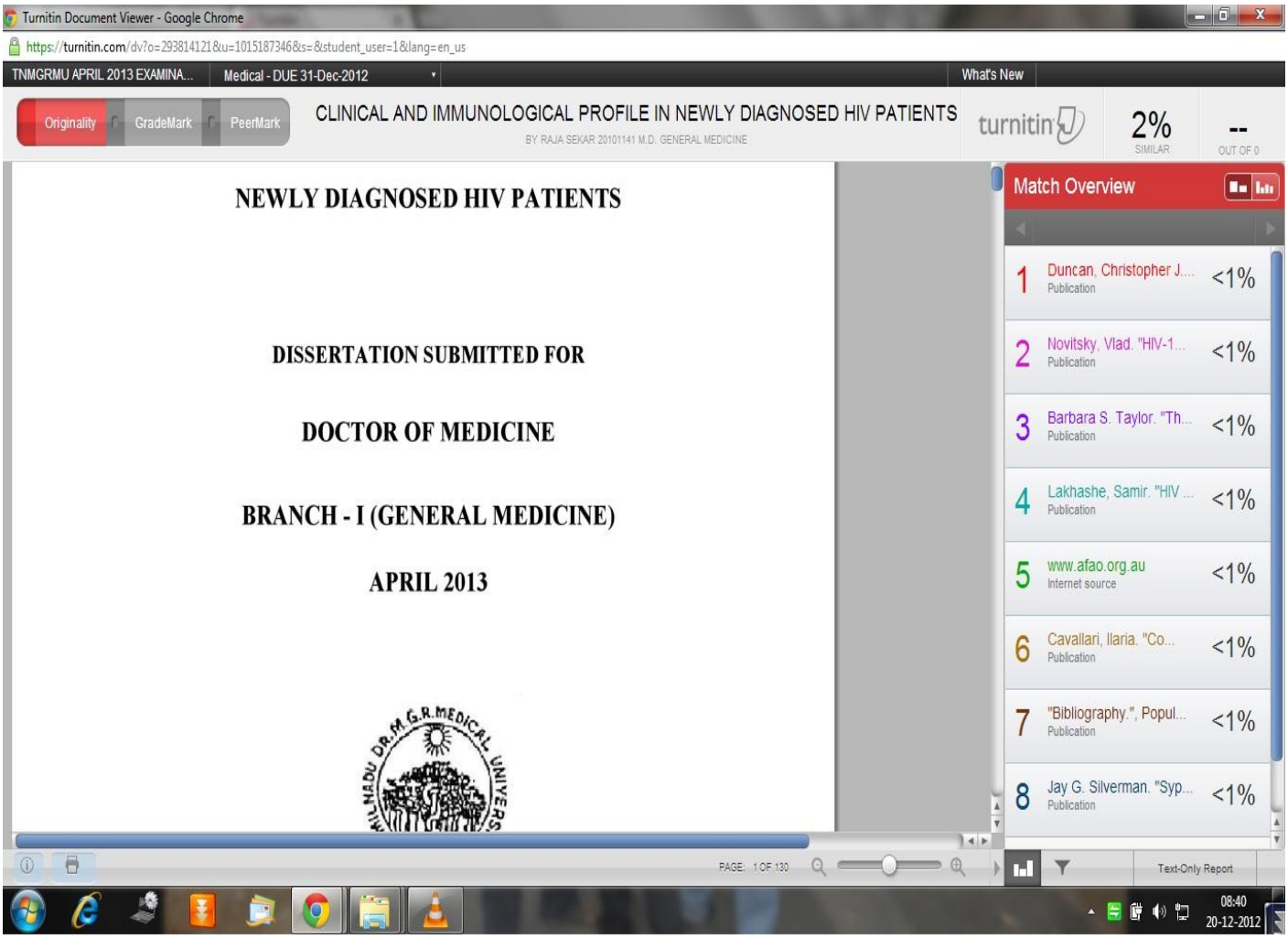
DEAN I/c

51/58

To

All the above members and Head of the Departments concerned.

All the Applicants.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